REMARKS

Claims 37-56 are pending in the present application.

In order to best familiarize the Examiner as to the state of the art in which Applicants have endeavored to provide the proper framework for analysis of the level of skill and expectation in the art, Applicants provide the following discussion:

Prior to the present invention, the state of the art in the field of veterinary science and in human sterility treatment is the use of *assisted reproductive technology* (ART). In ART, a spermatozoon and an ovum are first fertilized in vitro in a culture system to prepare a fertilized ovum. The fertilized ovum can be cultured via cleavage, morula and blastocyst stages to a hatching-blastocyst stage, and a late blastula stage (wherein a zona pellucida is denatured and disappeared). The fertilized ovum at the stages from cleavage to blastula stage may be transplanted in a uterus to faciltate production of a baby.

To this end, a fertilized ovum (a late blastula) is implanted on an endometrium in vivo. Subsequently, an inner cell mass (an embryoblast) grows to a development stage of early an embryo, including a gastrula forming process, which proceeds to a three-layer embryonic disc. However, heretofore, no reports exist that it is possible to facilitate such growth in a culture system.

Specifically, in culture systems that have been previously attempted, even if a fertilized ovum (a late blastula) is continuously cultured, only monolayer cells are proliferated *two-dimensionally*. Accordingly, proliferation of a three-dimensional architecture having an early embryo-like structure, such that a gastrula or a neurula is produced, has not been yet accomplished (specification at page 2, lines 13-17).

Despite advances in tissue engineering, only a basic reconstruction method has been

established for reconstituting organs (Ferber, D., Science 284, 422-425, (1999)). Hitherto, in order to construct a tissue by assembling cells and extracellular matrix components three-dimensionally, carriers having various forms from many materials have been developed. Further, the present inventors have already established a novel organ engineering method of reconstructing an organ-like construct by subjecting continuous three-step perfusion on an organ to remodel the organ into a culture version organoid (Japanese Patent Application Laid-open No. Hei 11-164684).

Although reports exist for reconstructing uterine gland-like structure by co-culturing human endometrial epithelial cells and stromal cells in a collagen gel, no reports currently exist of a culture carrier or a co-culturing carrier on which a fertilized ovum of an animal is cultured *to induce three-dimensional growth.*

In order to fill this void existing in the art, the present inventors developed a carrier for co-culturing a fertilized ovum of an animal composed of a cell incorporated type three-dimensionally reconstructed tissue in which cells are incorporated into a culture carrier. As such, the resultant carrier makes adhesion and three-dimensional growth of the fertilized ovum possible.

In short, for the purpose of providing a carrier for co-culturing as well as a method of culturing a fertilized ovum of an animal in which behavior of the fertilized ovum of an animal can be easily observed in a culture system and by which adhesion and three-dimensional growth of the fertilized ovum become possible, Applicants developed a method of using a cell-incorporated type three-dimensionally reconstructed tissue as a carrier for co-culturing the fertilized ovum of an animal. Such a discovery is not disclosed or suggested in art to which the invention relates and this discovery constitutes a surprising advance in the state of the art.

The rejection of Claims 4-6, 12, 15, and 27 under 35 U.S.C. §103(a) over Spaulding et al in view of Schinstine et al is obviated in part by amendment and traversed in part.

At the outset, Applicants note that the references cited in the outstanding Office Action reflect the state of the art prior to the present invention (discussed above and pages 1-4 of the present specification). At no point does the art of record disclose or suggest three-dimensional architecture having an early embryo-like structure such that a gastrula or a neurula is produced. At most, the references appear to suggest the blastocyst stages or the stage just before formation of gastrula.

Citing example 8, column 20, lines 29-56 of Spaulding et al, the Examiner asserts that this reference discloses that the endometrial tissue (which is comprised of epithelial cells and stromal cells) is co-cultured with the fertilized egg such that endometrial implantation constructs are formed that *support endometrial maturation until it is transplanted into a recipient uterus*. However, as discussed above, this statement supports that fact that Spaulding et al is merely similar to assisted reproductive technology (ART), which is distinct from the claimed invention.

Applicants direct the Examiner's attention to Example 1 of Spaulding et al in which constructs like cell-sheet are formed on a wall by rotation of bottle filled with cells. However, this is quite different from the claimed invention. In the present invention, cells are suspended in one or more gelated extracellular matrix components, e.g. collagen gel, mixed with mesh networks such as gauze and gelated to produce cell-sheet that inhibits contraction of the cell incorporated type three-dimensionally reconstructed tissue.

Moreover, the present invention relates to a carrier for co-culturing a fertilized ovum of an animal which comprises cell incorporated type three-dimensionally reconstructed tissue

that facilitates culturing while maintaining an implantation-like state and a culturing method of the fertilized ovum of an animal using the same. In this regard, the cell gel sheet containing mesh networks like gauze is removed from a culture vessel and floated in a culture medium to co-culture with a fertilized ovum. Thereby, epithelial cells like endometerium can be moved to contact with fertilized ovum, and that a layer of stromal cells and epithelial cell-like cells form gland-like structure within a gel at a distance from epithelial cells. Such an unexpected result is neither disclosed nor suggested by Spaulding et al.

Finally, Applicants wish to note that the structure obtained by the prior art methods (uterine gland-like structure) are nothing like three-dimensionally constructed tissue. As demonstrated in the examples of the present invention, epithelial-like cells take a three-dimensional tubular gland-like structure when using the claimed carrier. In contrast, in the prior art method, a simple gland-like structure is produced, and that this gland-like structure associates with epithelial like cells moved on collagen gel.

Schinstine et al is cited by the Examiner as disclosing application of mitomycin C for growth control of cell proliferation. However, at best, Schinstine et al may be used to demonstrate this aspect of the art, but in no way does this reference compensate for the aforementioned deficiencies in the disclosure of Spaulding et al. Specifically, Schinstine et al fail to describe a carrier for co-culturing of a fertilized ovum of an animal for the purpose of adhesion and three-dimensional growth of the fertilized ovum.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 8-9, 12, 14-16, 13, 19-31, and 34-35, under 35 U.S.C. §103(a) over Spaulding et al in view of Takezawa et al or Kumar is obviated in part by amendment and traversed in part.

In regard to Kumar, Applicants direct the Examiner's attention to the fact that this reference published on April 3, 2003, based on an application filed on September 4, 2002, which is a non-provisional of a U.S. provisional application filed on September 4, 2001. Since Kumar is an application for patent filed in the United States, it is (at best) entitled to a date as a reference under 35 U.S.C. §102(e) as of its effective U.S. filing date: September 4, 2001. However, the above-identified application was filed February 5, 2001, which is nearly 7 months prior to the effective filing date of Kumar. Therefore, Kumar is ***not*** prior art over the present application and has been improperly asserted as such. Accordingly, the rejection over the disclosure of Kumar should be withdrawn.

The Examiner cites Takezawa et al as disclosing the use of sterilized gauze immersed in vitrified type I collagen gel. However, this reference fails to compensate for the deficiencies in the disclosure of Spaulding et al as mentioned above. Accordingly, the collective disclosures of Spaulding et al coupled with Takezawa et al fail to disclose or suggest the claimed co-culturing carrier with a fertilized ovum of an animal comprising a cell incorporated type three-dimensionally reconstructed tissue for co-culturing the fertilized ovum of an animal for the purpose of adhesion and three-dimensional growth of the fertilized ovum.

Applicants request withdrawal of this ground of rejection.

The rejection of Claim 21 under 35 U.S.C. §103(a) over Spaulding et al in view of Goff and Smith is obviated in part by amendment and traversed in part.

In this ground of rejection, the Examiner cites Goff and Smith as disclosing the use of bovine endometrial cells for co-culture after IVF. However, as the Examiner recognizes, this reference merely discloses that bovine endometrial cells could maintain embryo development

to the blastocyte stage.

In contrast, as mentioned above, the present invention forms three-dimensional architecture such that a gastrula or a neurula is produced. This production occurs at a much later stage than blastocyte development. However, there is not disclosure or suggestion in Goff and Smith that bovine endometrial cells may serve in the capacity as presently claimed (i.e., three-dimensional growth of the fertilized ovum).

Moreover, Goff and Smith simply disclose that which is conventional in the art of the present invention (bovine endometrial cells for maintenance of embryo development to the blastocyte stage). However, this reference, even when used to supplement the disclosure of Spaulding et al, fails to disclose or suggest a carrier for co-culturing of a fertilized ovum of an animal enabling/for the purpose of adhesion and three-dimensional growth of the fertilized ovum.

Applicants request withdrawal of this ground of rejection.

The rejection of Claims 4-6, 8, 9, 12, 14-16, 21, 23, 27, 29-31, and 34-35 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Applicants note that the rejected claims have been canceled and, therefore, this ground of rejection is believed to be moot. Moreover, new Claims 37-56 are free of the Examiner's criticisms.

In view of the foregoing, Applicants submit that pending Claims 4, 5, 8, 21, 34, and 35 are definite within the meaning of 35 U.S.C. §112, second paragraph.

Applicants respectfully request withdrawal of this ground of rejection.

The objection to Claims 12, 14-16, and 21 is obviated by cancellation of previously pending claims. Applicants submit that the claims presented herein are free of the Examiner's criticisms. Acknowledgment that these grounds of objection have been withdrawn is solicited.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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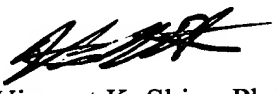

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